Support for the new claims is found throughout the specification and in the originally submitted claims. For example, the method operations depicted through Figures 3A, 4A 4B, and 4D depict the method and computer program operations set forth in the independent claims. Further, originally submitted claims 1, 6, and 17, for example, support the newly submitted independent claims. Dependent claims 90, 100, and 103 find support at page 10, lines 17-21. Dependent claims 91, 101, and 104 find support at pages 12-15. Dependent claims 92, 93, and 94 find support at in originally submitted claims 47, 49, and 53 respectively. Dependent claim 95 finds support at page 24, line 21 *et seq.* Dependent claim 96 finds support in original claim 33. Dependent claim 97 finds support at page 22, lines 19-21. Finally, dependent claim 98 finds support at page 21, liens 8-11.

Non Prior Art Issues

The Examiner has noted that some embedded hyperlinks or browser executable code remain in the specification after the amendment filed on September 10, 2001. The remaining hyperlink has been identified and removed by this amendment. Note that only one additional link could be located.

The previous claims were also rejected under 35 USC 112, 2nd paragraph for using the term "complement" with reference to "a plurality of single-stranded oligonucleotide or peptide subsequences . . . ." The new claims do not employ the term "complement." It is respectfully submitted that these claims are clear and definite and meet the requirements of 35 USC 112, 2nd paragraph.

Prior Art Rejection

The claimed methods and computer program products recite character strings that are themselves manipulated. In other words, character strings are transformed to other character strings by method operations or program code. Thus, the character strings of the claims are not merely representations of physical polynucleotides or polypeptides to be synthesized for a physical (wet chemical) nucleic acid recombination procedure. Nor are they merely representations of physical polynucleotides or polypeptides generated from such physical recombination procedure. Rather, they are computationally manipulated strings. Sequence information from the computational manipulations is then used to identify a set of oligonucleotides for *in vitro* recombination.

To meet the claim limitations, the prior art must suggest specific operations performed on character strings, and those operations must cause a transformation of the character strings. In addition, the prior art must suggest using the transformed character strings to identify oligonucleotides for a subsequent *in vitro* process.

In the final office action preceding this filing, the Examiner relies on the Zhao et al. reference (Nature Biotechnology, Vo. 16:258-261, March 1998). In making the rejection, the Examiner provided only the following remark:

> It is well-known that nucleic acids and polypeptides are represented by letters or characters, for example, A, T, G and C for nucleotides. Since Zhao et al. conducted the actual recombination of nucleic acids and since such nucleic acids are represented by letter like A, T, G and C, it would have been obvious to [a person of] ordinary skill in the art that such recombination can be represented by recombination of character strings, i.e. strings of A, T, G, and/or C.

The Zhao et al. article does not describe using character strings. It describes using actual nucleic acids in an *in vitro* procedure. In making his rejection, the Examiner may be arguing that the researchers who authored the Zhao et al. article likely knew the sequences of their nucleic acids and likely also recorded those sequences as character strings. If this is the case, the Examiner should find the newly submitted claims distinguishable, as they recite specific manipulations of character strings – which manipulations are nowhere suggested in the reference and in all likelihood would not have been performed by the authors.

Alternatively, the Examiner may be arguing that, generally, any physical process performed on character strings is unpatentable over any prior art that describes the same process performed on actual nucleic acids. If this is the case, then the Examiner should find at least newly submitted claims 89-98 distinguishable as they require both computational and *in vitro* operations. Specifically, the claims require (1) a manipulation of character strings (application of a genetic operator and selection of substrings) to identify physical oligonucleotides for recombination and then (2) actual recombination of the physical oligonucleotides. No prior art known to Applicants employs the recited character manipulation (or a corresponding physical manipulation) to identify and then generate the physical oligonucleotides and subsequent recombination of those oligonucleotides.

Because the claims cover methods and program instructions for transitioning from the character string domain to the physical domain, they do not constitute a mere character

representation of a corresponding physical process. They employ specific character string manipulations to identify oligonucleotide sequences for a separate *in vitro* recombination procedure.

To elaborate, claim 89 to 98 recite a method having both computational and *in vitro* components. Claims 99 to 104 recite the computational components used to identify oligonucleotides for subsequent *in vitro* recombination. In all claims, the computational components include (a) manipulation of a parent character string to generate a derivative character string and (b) selection of at least one character substring from the derivative character string.

The method described in the Zhao et al. reference does not employ a comparable *in vitro* or character string manipulation. In the reference, the choice of oligonucleotides for recombination does not depend on selecting a subsequence or substring from a derivative sequence or character string. The Zhao et al. reference simply describes an *in vitro* method for assembling chimeric genes from template sequences (two thermostable subtilisin E genes) and primers exposed to repeated cycles of denaturation and abbreviated annealing/polymerase-catalyzed extension. Gradually, over the repeated cycles, chimeric extension products result. So rather than identifying subsequences, the process identifies the opposite, extension products. The reference does not explain how the primers are identified. Nothing in the reference suggests that the primers should be selected by character string manipulations of the types recited in the claims.

Focusing again on the Office Action, the only support for the section 103 rejection is the bald assertion that "it would have been obvious to one of ordinary skill in the art that such recombination [the *in vitro* recombination described the Zhao et al. article] can be represented by recombination of character strings." Applicants acknowledge that representing nucleic acids and polypeptides by character strings is well known. But representing *in vitro* transformations of nucleic acid sequences serves little useful purpose. The acts of tracking each recombination step of an *in vitro* process, obtaining the sequences of the nucleic acid participants in the recombination steps, and reducing those sequences to character strings would be a tiresome and wholly unsatisfying task. One of skill in the art would have little or no motivation to provide a character string account of the *in vitro* recombination described in the Zhao et al. reference. Absent a showing that the prior art motivates one of skill in the art to provide such character string account of the Zhao et al. reference's *in vitro* recombination, a section 103 rejection is not, in Applicants' understanding, proper.

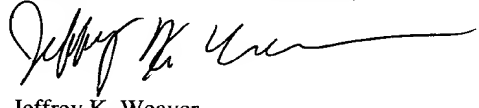
It is worth noting that the character string manipulations of the claimed invention provide certain benefits over *in vitro* methods. These benefits result from performing some operations with character strings rather than actual physical sequences. For example, all genetic operators,

including various types of mutagenesis and crossovers can be fully and independently controlled in a reproducible fashion, removing the human error and variability inherent in physical manipulations of nucleic acids. Further, sequences from inaccessible or non-cultivatable organisms can be used in character string manipulations. Also, certain undesirable physical results such as frame shift mutations and premature terminations are discarded from the character set or repaired, therefore avoiding wasted laboratory effort. Still further, the character string manipulations do not rely any level of sequence identity, as the prior art *in vitro* methods rely.

In summary, the Zhao et al. reference does not suggest manipulating character strings in the manner claimed. And the Zhao et al. reference does not suggest manipulating nucleic acids in that manner. Also, the Zhao et al. reference does not suggest a method that proceeds from the character string domain to the physical oligonucleotide domain. Applicants know of no prior art that suggests a character string manipulation, like the one claimed, that identifies oligonucleotides for an *in vitro* recombination. Finally, a prior art *in vitro* method of nucleic acid manipulations does not render a corresponding computational method of character string manipulations unpatentable. The prior art provides no motivation for a skilled person to represent the in vitro methods by character string manipulations.

For the above reasons, it is respectfully submitted that claims 89-104 are allowable over the prior art. Applicants respectfully request a Notice of Allowance for this application. Should the Examiner believe that a telephone conference would expedite the prosecution of this application, the undersigned can be reached at the telephone number set out below.

Respectfully submitted,
BEYER WEAVER & THOMAS, LLP



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MARKED UP PARAGRAPHS ILLUSTRATING THE AMENDMENTS MADE TO THE SPECIFICATION OF 09/494,282 WITH ENTRY OF THIS AMENDMENT

Please delete the paragraph beginning at page 49, line 30 and ending at page 50, line 7 and substitute therefor the following new paragraph:

HMM can be used in other ways as well. Instead of applying the generated profile to identify previously unidentified family members, the HMM profile can be used as a template to generate de novo family members (e.g., intermediate members of a cladistic tree of nucleic acids). For example, the program, HMMER is available [(**http://hmmer.wustl.edu/**)] **at hmmer.wustl.edu (on the world wide web)**. This program builds a HMM profile on a defined set of family members. A sub-program, HMMEMIT, reads the profile and constructs de novo sequences based on that. The original purpose of HMMEMIT is to generate positive controls for the search pattern, but the program can be adapted to the present invention by using the output as in silico generated progeny of a HMM profile defined shuffling. According to the present invention, oligonucleotides corresponding to these nucleic acids are generated for recombination, gene reconstruction and screening.